

Liver Function Tests in Workers with Occupational Exposure to Polychlorinated Biphenyls (PCBs): Comparison with Yusho and Yu-Cheng

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The results of liver function tests in a population manufacturing capacitors and transformers are presented. Two clinical field examinations were performed, one in 1976 when PCBs were still used in the manufacturing of the electrical equipment and one at the end of 1979, 2.5 years after discontinuation of PCBs use. A low prevalence of abnormal liver function tests was found and mean values for all tests were within normal laboratory ranges. At the initial examination, weak, but statistically significant correlations were found between log LDH and plasma levels of log HPCB (higher chlorinated congeners of polychlorinated biphenyls) and log TPCB (total polychlorinated biphenyls) among the female workers, while log γ -GTP correlated significantly only with log HPCB among the male workers. A significant increase to abnormal levels of γ -GTP was noted at the follow-up examination in both male and female workers, and preliminary results indicate significant correlations between γ -GTP and serum levels of PCBs among the male workers.

These findings are in accordance with previously reported data on populations occupationally exposed to PCBs, but differ from hepatic biochemistry findings in accidental poisonings due to ingestion of cooking oil contaminated with PCBs and related compounds, i.e., polychlorinated dibenzofurans (PCDFs) and polychlorinated quaterphenyls (PCQs). Hence, the importance of considering the related compounds as etiologic factors in PCB poisoning is emphasized.

Introduction

Polychlorinated biphenyls (PCBs), a group of chemicals consisting of complex mixtures of chlorinated biphenyls (1), have been used industrially since the late 1920s. Their chemical stability and nonconductor qualities have rendered them very useful as dielectric fluids in capacitors and transformers. They have also been used in hydraulic systems and as additives in paints, surface coatings, and in carbonless copy papers.

The widespread contamination of the human environment by PCBs was reported in 1966 (2), and concern over possible harmful effects on human health caused manufacturing of PCBs in the United States to be discontinued in 1977 (3,4).

There is extensive literature reporting toxic effects of PCBs on various organ systems in experimental animals (5). A wide spectrum of hepatic abnormalities have been observed, including hepatic enlargement and weight increase related to hepatic cell hypertrophy and

increase in the smooth endoplasmic reticulum (6); nodular hyperplasia and hepatocellular carcinoma have also been observed in PCB-treated certain strains of rats and mice (7,8). Association between hepatic effects and degree of chlorination, has also been suggested (9).

In contrast, effects of PCBs on humans are more uncertain, but liver function abnormalities have been reported with either accidental or occupational exposures to PCBs. Early studies involving occupational exposure reported acute hepatic disease, i.e., acute yellow atrophy (10,11). Abnormal liver function tests were also found in patients with severe "Yusho", representing the first major outbreak of PCBs poisoning (12). Similar findings were reported in patients from a second epidemic of PCB intoxication ("Yu-Cheng") in Taiwan (13). (Names given to the diseases observed in connection with two major epidemics of poisoning due to ingestion of oil contaminated with PCBs and related compounds. Yusho is Japanese for "oil disease" and Yu-Cheng is the Chinese rendering of the same.) Nevertheless, more recent investigations of occupationally exposed populations report absence of clinically manifest hepatic dysfunction in general (14-17). Attention has been directed

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to the role of polychlorinated dibenzofurans (PCDFs) and polychlorinated quaterphenyls (PCQs) as etiologic factors causing "PCB-associated" disease (18). In this context, one should consider that simultaneous exposure to other chlorinated compounds, i.e., chlorinated naphthalenes, occurred in workers exposed to PCBs, who developed acute yellow atrophy of the liver (10, 11, 19). This condition has been reported in workers with exposure to chlorinated naphthalenes alone (20).

In this communication, we present the results of liver function tests in a group of workers manufacturing capacitors and transformers and discuss these findings in relation to observations made in Yusho and Yu-Cheng.

Materials and Methods

In order to investigate health effects associated with long-term occupational exposure to PCBs, a cross-sectional study was conducted in March 1976 on 326 workers employed at two facilities where capacitors were manufactured. PCB-containing dielectric fluid had been used at the plants since the late 1940s, and there was potential for exposure along most of the production line. Different PCB mixtures had been used over the years. During the 1940s and 1950s, the dielectric fluid consisted primarily of PCB compounds with higher chlorinated congeners (HPCB), such as Aroclor 1254 and 1242. In contrast, since 1972, i.e., 4 years prior to the initial phase of the study, lower chlorinated PCBs (LPCB) such as Aroclor 1016 and 1221, had been the main compounds used in the manufacturing process. In addition to PCBs, the dielectric fluid contained chlorinated benzenes and an epoxide compound used as a stabilizer. The intensity of exposure ranged from mean air levels of 0.007 mg/m air in areas with the lowest exposures to 0.41 mg/m in departments where more direct contact with the fluid was required, as in the testing of equipment and in the quality control area. Air levels of 0.9 mg/m and 11.0 mg/m were measured in areas where equipment was immersed in the dielectric fluid or washed.

Exposure occurred mainly from inhalation of fumes released from heated fluid, but both skin contact and ingestion may have been significant routes of entry as well.

The population was selected from a total workforce of approximately 800 individuals. The most important criterion for inclusion in the study group was employment for ten or more years, but some individuals with less than 10 years of employment who came for examination were also included. All were volunteers. Methodological aspects of this investigation have been summarized elsewhere (21).

PCB determinations were done by gas chromatography (22) on plasma samples (initial study) and serum samples (follow-up study) obtained from venous blood samples. PCB levels were initially available for analysis on 289 individuals. Liver function tests included γ -glutamyl transpeptidase (γ -GTP), serum glutamic-oxala-

cetic transaminase (SGOT), serum glutamic-pyruvic transaminase (SGPT), alkaline phosphatase (alk. phos.), lactic dehydrogenase (LDH) and bilirubin. These were all measured by a sequential multiple auto analyzer system.

Excluded from the analysis were subjects with a history of the following: using oral contraceptives or other sex hormones, steriods, excessive alcohol consumption, jaundice, infectious hepatitis, and enlarged liver. These individuals were excluded because of potential interference and confounding effects on liver function. Thus, 261 individuals were included in the analysis. Twenty-eight retired workers were initially excluded in the correlational analyses between "current exposure" and biological parameters. However, the effect of their inclusion was also investigated (see below in Results).

The use of PCBs was discontinued in the manufacturing facilities in July 1977, and industrial hygiene surveys conducted during the period between the studies provided evidence that there had been a marked decrease in air levels of PCBs (23). A mixture of dioctyl phthalate and chlorinated benzenes replaced the PCBs containing compound as dielectric fluid. Follow-up examination of 194 subjects was performed in December 1979, three years and nine months after the initial study.

Statistical analysis was undertaken, using the Statistical Analysis System (SAS) and the Statistical Package for the Social Sciences (SPSS). Because of the distribution of the data, logarithmic transformations were used in the statistical correlations.

Differences in mean values were calculated by Student's *t*-test for paired data and changes in liver function tests from normal to abnormal range were calculated by McNemar's test of symmetry. Associations between PCB levels and liver function tests were calculated by Fisher's exact test.

Results

Initial Study

The duration of employment, shown in Table 1, demonstrates that 68% of the subjects had been employed for 10 years or longer; 37% had 20 or more years' duration of employment; 64% were 40 years of age or older. The age and sex distributions of the examined workers are shown in Table 2.

Plasma PCB concentrations of the examined workers

Table 1. Duration of employment of 260 workers manufacturing capacitors.

| Duration, yr | Male workers | | Female workers ^a | | Total workers | |
|--------------|--------------|-----|-----------------------------|-----|---------------|-----|
| | No. | % | No. | % | No. | % |
| 0-9 | 59 | 41 | 24 | 21 | 83 | 32 |
| 10-19 | 34 | 23 | 46 | 40 | 80 | 31 |
| >20 | 53 | 36 | 44 | 39 | 97 | 37 |
| Total | 146 | 100 | 114 | 100 | 260 | 100 |

^aDuration of employment not available for one female worker.

(Table 3) indicated a high prevalence of elevated PCB levels suggesting significant absorption in the majority of subjects. For 35% of the workers the LPCB level was 100 ppb or higher, while 44% had HPCB concentration of 25 ppb or higher.

Mean values of the liver function tests and prevalences of abnormal levels are shown in Tables 4 and 5. Although significant differences in liver function tests were found between male and female workers, the mean values were well within normal limits for all tests. Moreover, the prevalence of abnormal liver function tests was comparable with that reported in a study of a general population (24).

No significant correlation was found between any of the liver function tests and duration of employment.

Table 2. Age distribution of 261 workers manufacturing capacitors.

| Age | Male workers | | Female workers | | Total workers | |
|-------|--------------|-----|----------------|-----|---------------|-----|
| | No. | % | No. | % | No. | % |
| 20-39 | 68 | 47 | 24 | 21 | 92 | 36 |
| 40-49 | 44 | 30 | 32 | 28 | 76 | 29 |
| 50-59 | 28 | 19 | 54 | 47 | 82 | 31 |
| >60 | 6 | 4 | 5 | 4 | 11 | 4 |
| Total | 146 | 100 | 115 | 100 | 261 | 100 |

Table 3. Plasma concentrations of lower (LPCB) and higher (HPCB) homologs of PCBs in 230 workers manufacturing capacitors.*

| Type of PCB | Concn, ppb | Male workers | | Female workers | | Total workers | |
|-------------|------------|--------------|-----|----------------|-----|---------------|-----|
| | | No. | % | No. | % | No. | % |
| LPCB | 0-99 | 85 | 62 | 66 | 70 | 151 | 65 |
| | 100-199 | 28 | 21 | 17 | 18 | 45 | 20 |
| | > 200 | 23 | 17 | 11 | 12 | 34 | 15 |
| | Total | 136 | 100 | 94 | 100 | 230 | 100 |
| HPCB | 0-24 | 68 | 50 | 60 | 64 | 128 | 56 |
| | 25-74 | 50 | 37 | 24 | 26 | 74 | 32 |
| | > 75 | 18 | 13 | 10 | 10 | 23 | 12 |
| | Total | 136 | 100 | 94 | 100 | 230 | 100 |

*Plasma PCB concentrations not available on 31 workers, 10 males and 21 females

Only one significant correlation was found between age and a liver function test, namely, with alkaline phosphatase, and this was observed solely among the male workers.

Pearson correlation coefficients between liver function tests and plasma PCB levels are shown in Table 6. Significant correlations were limited to those between log LDH vs. log HPC and log TPC, and between log γ -GTP and log HPCB. While "statistically significant," the correlation coefficients were low. When liver function tests were computed against PCB levels applying Fisher's exact test, significant associations were found between SGOT and both HPCB and LPCB. This association was only significant for the female workers; the small number of abnormal observations should not be overlooked (Tables 7 and 8).

Since this analysis addressed only actively employed workers, it was of interest to investigate whether the inclusion of 28 retirees (11 males and 17 females) would significantly influence the correlational study. The inclusion of these individuals eliminated the previously observed significant correlations between log γ -GTP and log HPCB in the male workers and also rendered the correlation between log LDH and log TPCB observed among the female workers nonsignificant. The association between SGOT and both HPCB and LPCB observed among the female workers remained the same.

Follow-up Examination

At the present time, the analysis of the data from the follow-up examination is in progress, and the observa-

Table 4. Liver function test results (mean \pm SD) in 144 male workers and 112 female workers manufacturing capacitors.*

| Test | Female workers Mean \pm SD | Male workers Mean \pm SD |
|----------------------------|---------------------------------|-------------------------------|
| SGOT, IU/L | 24.8 \pm 11.4 | 27.1 \pm 10.8 |
| SGPT, IU/L | 25.5 \pm 13.1 | 31.2 \pm 13.5 |
| Alkaline phosphatase, IU/L | 25.6 \pm 8.7 | 26.2 \pm 6.9 |
| LDH, IU/L | 175.9 \pm 30.8 | 167.1 \pm 25.7 |
| λ -GTP, μ L | 10.8 \pm 7.5 | 15.7 \pm 9.0 |

*Retirees excluded.

Table 5. Liver function test results in 261 capacitor manufacturing workers.

| | Male workers | | Female workers | | Total workers | |
|----------------------------|-------------------|---------------------|-------------------|---------------------|-------------------|---------------------|
| | Normal No. (%) | Abnormal No. (%) | Normal No. (%) | Abnormal No. (%) | Normal No. (%) | Abnormal No. (%) |
| SGOT, IU/L | < 50 142(97) | \geq 50 4(3) | < 50 113(98) | \geq 50 2(2) | < 50 255(98) | \geq 50 6(2) |
| SGPT, IU/L | < 50 134(92) | \geq 50 12(8) | < 50 108(94) | \geq 50 7(6) | < 50 242(93) | \geq 50 19(7) |
| LDH, IU/L | < 250 145(99) | \geq 250 1(1) | < 250 111(97) | \geq 250 4(3) | < 250 256(98) | \geq 250 5(2) |
| Alkaline phosphatase, IU/L | < 50 145(99) | \geq 50 1(1) | < 50 113(98) | \geq 50 2(2) | < 50 258(99) | \geq 50 3(1) |
| γ -GTP, μ L | < 40 143(98) | \geq 40 3(2) | < 40 113(98) | \geq 40 2(2) | < 40 256(98) | \geq 40 5(2) |
| Bilirubin, mg/100 mL | < 1.2 146(100) | \geq 1.2 0(0) | < 1.2 115(100) | \geq 1.2 0(0) | < 1.2 261(100) | \geq 1.2 0(0) |

Table 6. Pearson correlation coefficients between liver function tests and plasma PCBs levels in 93 female workers and 134 male workers manufacturing capacitors.^{a,b}

| | log (LPCB) | log (HPCB) | log (TPCB) |
|----------------------|-----------------|----------------------|----------------------|
| Females | | | |
| log (SGOT) | 0.126 (0.228) | 0.049 (0.638) | 0.105 (0.316) |
| log (SGPT) | 0.135 (0.197) | 0.089 (0.396) | 0.120 (0.251) |
| log (alk. phos.) | - 0.032 (0.758) | 0.144 (0.169) | 0.015 (0.885) |
| log (LDH) | 0.182 (0.080) | <i>0.240 (0.021)</i> | <i>0.213 (0.040)</i> |
| log (γ -GTP) | - 0.168 (0.107) | - 0.112 (0.286) | - 0.173 (0.097) |
| log (bilirubin) | 0.062 (0.551) | 0.017 (0.877) | 0.040 (0.702) |
| Males | | | |
| log (SGOT) | 0.117 (0.179) | 0.118 (0.175) | 0.127 (0.143) |
| log (SGPT) | 0.066 (-0.449) | - 0.007 (0.936) | 0.058 (0.505) |
| log (alk. phos.) | - 0.092 (0.288) | - 0.003 (0.972) | - 0.065 (0.453) |
| log (LDH) | 0.004 (0.961) | 0.079 (0.366) | 0.019 (0.828) |
| log (γ -GTP) | - 0.010 (0.912) | <i>0.175 (0.043)</i> | 0.059 (0.497) |
| log (bilirubin) | 0.065 (0.452) | 0.089 (0.315) | 0.021 (0.803) |

^aP values are in parentheses. Significant correlations are italic.

^bRetirees excluded.

tions presented on a subset of 105 individuals of the study population are preliminary and limited to the liver function tests. (Changes in serum concentrations of PCBs over the 45-month period that elapsed between the two clinical field examinations will be reported elsewhere.) Although there was a significant decrease in mean values of most liver function tests, namely SGOT, SGPT, bilirubin and LDH, a significant increase in mean concentrations were noted for γ -GTP and alkaline phosphatase. However, only for γ -GTP was significant alteration from normal to abnormal range noted. For this variable, the increase in abnormal levels was highly significant (χ^2 (McN) = 25.04, $p < 0.001$). Moreover, significant correlations were found among the male workers between log γ -GTP and log LPCB, log HPCB and log TPCB. The Pearson correlation coefficients were 0.34 ($p = 0.02$), 0.39 ($p = 0.007$) and 0.38 ($p = 0.01$), respectively. [At the initial examination, low but significant correlation was only noted between log γ -GTP and log HPCB ($r = 0.18$, $p = 0.04$)]. Significant correlation was also noted between log SGPT and log HPCB among the male workers ($r = 0.31$, $p = 0.04$), again a change from the initial examination. There were no significant correlations between any of the liver function tests and serum levels of PCBs among the female workers hitherto re-examined. Inclusion of retirees in the above calculations eliminated all the significant correlations between liver function tests and PCB levels.

Discussion

Although there is ample evidence of the hepatic effects of PCBs in experimental animals, liver abnormalities in humans have been less well characterized.

Clinical syndromes thought to be characteristic of PCB poisoning were reported in connection with two major accidents involving ingestion of PCB-contaminated cooking oil. The first was the so-called Yusho (Japanese

Table 7. Distribution of SGOT levels by HPCB categories in 93 female workers manufacturing capacitors.^a

| HPCB | SGOT normal Number (%) | SGOT abnormal Number (%) | Total |
|-----------|---------------------------|-----------------------------|-------|
| ≤ 75 | 83 (100) | 0 (0) | 83 |
| > | 8 (80) | 2 (20) | 10 |
| Total | 91 | 2 | 93 |

^aFisher's exact test (one-tail): $p = 0.01$.

Table 8. Distribution of SGOT levels by LPCB categories in 93 female workers manufacturing capacitors.^a

| LPCB | SGOT normal Number (%) | SGOT abnormal Number (%) | Total |
|------------|---------------------------|-----------------------------|-------|
| <200 | 83 (100) | 0 (0) | 83 |
| ≥ 200 | 8 (80) | 2 (20) | 10 |
| Total | 91 | 2 | 93 |

^aFisher's exact test (one-tail): $p = 0.01$.

for "oil disease") episode. Initial studies on Yusho patients did reveal abnormalities in routine liver function tests in severe cases. Also, hepatomegaly was found in some patients. Although no light microscopic changes were revealed in hepatic biopsy specimens from a Yusho patient, electron microscopic analysis did show alterations in the endoplasmic reticulum and in the mitochondria (12). It has been suggested that these changes may be morphological manifestations related to enzyme induction caused by PCBs, which has been demonstrated in both experimental and clinical studies (25,26). Analogously, there was a high prevalence of abnormal liver function tests, i.e., SGOT, SGPT and alkaline phosphatase, among 36 patients with severe signs of intoxication in connection with a second major accidental intoxication episode in Taiwan known as Yu-Cheng (27).

Abnormalities in liver function have been reported in populations employed in PCBs-related occupations, but in most studies, liver function abnormalities have been mild, and overt clinically significant liver disease as reflected by anamnesis and physical examination, has rarely been reported. (14-17,28) One exception is the study by Maroni et al. (29), reporting a high prevalence of biochemical liver abnormalities and hepatomegaly on physical examination. Nevertheless, even in studies reporting a low prevalence of liver abnormalities, significant correlations have been found between serum PCB levels (both HPCB and LPCB), SGOT and γ -GTP (15,16).

In the present investigation, liver function tests in workers employed in capacitor and transformer manufacturing were studied. Few abnormalities were observed, and mean values for liver function tests were within normal laboratory limits. Inclusion of retired employees did not add to the prevalence of liver function abnormalities, but rather eliminated two significant correlations, namely between log LDH and log TPCB in the female workers, and the correlation between log γ -GTP and log HPCB among the male workers. Significant association between SGOT levels and serum levels of both HPCB and LPCB were found for the total population (males and females), but the association re-

mained significant only for the female workers when analyzed separately. However, the small number of abnormal liver function observations should be recognized in this context. Preliminary data from a follow-up study indicated a significant increase in the prevalence of abnormal values of γ -GTP, and significant correlations were found between γ -GTP and serum levels of PCBs among the male workers. Inclusion of retirees in the calculations eliminated the statistical significance of these correlations.

It is evident from our data that there is a difference in severity of clinical manifestations between patients with either Yusho or Yu-Cheng and those with effects of occupational exposure to PCBs. This "discrepancy" is interesting, since occupationally exposed individuals studied have had higher serum or plasma PCB levels in general than the typical patients. In discussing this discrepancy, it would seem pertinent to consider the possibility that contaminants may play an important causative role in the pathogenesis of PCB poisoning (30). During the past decade, evidence has accumulated that the rice oil ingested by patients with Yusho also contained polychlorinated dibenzofurans (PCDFs) and polychlorinated quaterphenyls (PCQs). Both have been found in the blood and other organs of the Japanese patients (31,32). Similar observations have been made in Taiwanese patients (33). It is also of interest that experiments on primates using a mixture of PCDFs similar to those in the Japanese oil showed both dermatological and systemic changes suggestive of Yusho, but that the administration of PCBs or PCQs alone failed to induce such changes in either primates or rats (31). A recent study on three PCB-exposed occupational groups in Japan followed over a 5-year period can be considered as a clinical correlate to these observations in experimental animals. Despite high plasma PCB levels, hepatic function was reported normal. Plasma concentration of PCQs in two of the occupational groups examined were the same as in the general nonexposed population (34).

Although levels of PCDFs and other contaminants are unavailable on our study population at the present time, it seems apparent from our observations and the results of the Japanese study of PCB-exposed workers, (34) that the mere presence of a high plasma or serum level of PCBs (in the absence of significant levels of PCDFs and/or PCQs) is not necessarily associated with overt clinical liver disease. It is still possible, however, that "subclinical" alterations are present in such workers as suggested by the enzyme-inducing capacity of PCBs (26). Our findings are also in accordance with currently prevailing concepts of several authors that PCDFs, PCQs and perhaps other contaminants such as chlorinated diphenyl ethers, should be considered as important etiological factors in clinical "PCB poisoning" (18,30-34).

The increase in prevalence of abnormal levels of γ -GTP observed between our original and follow-up examinations is intriguing. A correlation was found be-

tween γ -GTP and serum levels of PCBs among the male workers not previously observed in our initial study. Further analysis is in progress in order to clarify whether these findings might be related to changes in the work environment as a result of discontinuing the use of PCBs with subsequent metabolic implications in terms of altered pharmacokinetics of PCBs, and the introduction of replacement materials.

Mortality studies of PCB-exposed workers have been suspect but have not yet provided conclusive evidence of an increased risk of liver cancer. However, two cases of hepatic cell carcinoma have been reported in autopsy examinations of 12 "Yusho" patients (35,36). Additional observations are necessary to clarify an etiological relationship between PCB-related occupations and the development of hepatic disease.

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